Institution: University of Exeter		
Unit of Assessment: UoA 1 Clinical Medicine		
Title of case study: Genetic test improves prediction of type 1 diabetes, treatment decisions and enhances clinical trials		
Period when the underpinning research was undertaken: 2005 to date		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Michael Weedon Richard Oram	Associate Professor Associate Professor & Honorary Renal Consultant	2005-2020 2010-2020
Period when the claimed impact occurred: 2016-2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

A simple, cheap and robust genetic test developed at the University of Exeter is being used to predict and classify type 1 diabetes. The test has been adopted by NHS diagnostic services in England and Scotland to **improve diabetes classification**, and by two health systems in the United States, for studies screening thousands of newborns for their risk of the disease. It is also being used to screen 500,000 newborns for their suitability to take part in the first early-life pan-European trial of a type 1 diabetes vaccine and has helped to halve the cost of these trials, by selecting participants who are twice as likely to develop type 1 diabetes.

By screening for type 1 diabetes risk from birth, the test plays a key role in **preventing a life-threatening metabolic disorder** called ketoacidosis in infants. The test also helps to classify an individual's specific subtype of diabetes, guiding decisions about whether they need to be treated with insulin, tablets, or not at all. The Exeter team has **partnered with global healthcare company** Randox, which has already invested around £200,000 in the development of the test into a diagnostic biochip, to meet rising demand.

2. Underpinning research

Exeter is a world-leading centre for diabetes research, and over the past 15 years has pioneered the use of common genetic variants to predict and classify different types of diabetes. Type 1 diabetes, for example, occurs when the body produces too little of the hormone insulin, causing dangerously high blood sugar levels. In contrast, type 2 diabetes occurs when the body develops resistance to insulin.

2.1. A genetic risk score improves discrimination between type 1 and type 2 diabetes, and monogenic diabetes

Exeter researchers developed a type 1 diabetes genetic risk score (T1D GRS) that sums 30 common genetic risk variants for type 1 diabetes into a single metric, to aid in the classification of diabetes subtypes. It is extremely important to classify diabetes type correctly, to ensure correct treatment. For example, individuals with type 1 diabetes require insulin injections, but those with type 2 diabetes can commonly be managed with tablets and a controlled diet. The researchers demonstrated that their T1D GRS could discriminate between these two major diabetes subtypes with an accuracy of 87% (clinically useful tests usually require an accuracy over 80%) [**3.1**].

When this GRS was combined with an analysis of existing biomarkers, it provided an overall discrimination accuracy of 97%, even in cases that were hardest to classify. The Exeter team subsequently demonstrated that the score could similarly discriminate between type 1 and monogenic diabetes — a rare subtype caused by a single genetic mutation that

accounts for about 3.6% of diabetes diagnoses in patients under 30 years of age, with more than 15,000 cases in the UK [**3.2**].

2.2. A type 1 diabetes genetic risk score can identify high-risk newborn babies for inclusion in clinical trials

The T1D GRS can identify infants, children and adults who have a very high risk of developing type 1 diabetes [**3.3, 3.4**]. The Exeter researchers defined T1D GRS values that corresponded to a high (>10%) future risk of type 1 diabetes in infants [**3.4**]. The researchers recently improved their initial T1D GRS to identify newborns at >20% risk of type 1 diabetes in childhood [**3.5**].

2.3. The type 1 diabetes genetic risk score can be used for population-wide prediction of future rates of type 1 diabetes

The relatively rare prevalence (about 0.3-0.5% of the population) of type 1 diabetes means that a genetic risk assessment alone cannot be used to predict who will develop the disease — even among high-risk individuals, most will not develop type 1 diabetes [**3.5**]. However, the Exeter team has developed a combined approach using genetic risk and longitudinal autoantibody monitoring that more accurately predicts type 1 diabetes and makes screening feasible.

The researchers first demonstrated this approach in a study of first-degree relatives [**3.4**], and more recently developed a prediction model that can be applied from birth, based on a study of roughly 7,000 children who were monitored periodically for the first 10 years of their lives [**3.6**]. The combined risk score integrates the T1D GRS with family history and autoantibody status to provide an accurate prediction of disease onset, with a time-dependent discrimination accuracy of more than 90% from 2-8 years of age [**3.6**]. The team used this model to develop a population screening strategy that halves the typical number of healthcare visits needed to identify 75% of childhood type 1 diabetes cases before diagnosis [**3.6**].

3. References to the research

3.1. Oram, R.A., Patel, K., Hill, A., Shields, B., McDonald, T.J., Jones, A., Hattersley, A.T. & **Weedon, M.N**. (2016) A Type 1 Diabetes Genetic Risk Score Can Aid Discrimination Between Type 1 and Type 2 Diabetes in Young Adults. *Diabetes Care* 39(3), 337-344. DOI: 10.2337/dc15-1111

3.2. Patel, K.A., **Oram, R.A.,** Flanagan, S.E., De Franco, E., Colclough, K., Shepherd, M., Ellard, S., **Weedon, M.N.** & Hattersley, A.T. (2016) Type 1 Diabetes Genetic Risk Score: A Novel Tool to Discriminate Monogenic and Type 1 Diabetes. *Diabetes* 65(7), 2094-2099. DOI: 10.2337/db15-1690

3.3. Bonifacio, E., Beyerlein, A., Hippich, M., Winkler, C., Vehik, K., **Weedon, M.N.**, Laimighofer, M., Hattersley, A.T., Krumsiek, J., Frohnert, B.I., Steck, A.K., Hagopian, W.A., Krischer, J.P., Lernmark, Å., Rewers, M.J., She, J.X., Toppari, J., Akolkar, B., **Oram, R.A.**, Rich, S.S., Ziegler, A-G. & TEDDY Study Group. (2018) Genetic scores to stratify risk of developing multiple islet autoantibodies and type 1 diabetes: A prospective study in children. *PLoS Med*. 15(4), e1002548. DOI: 10.1371/journal.pmed.1002548

3.4. Redondo, M.J., Geyer, S., Steck, A.K., Sharp, S., Wentworth, J.M., **Weedon, M.N.**, Antinozzi, P., Sosenko, J., Atkinson, M., Pugliese, A. & **Oram, R.A.** (2018) Type 1 Diabetes TrialNet Study Group. A Type 1 Diabetes Genetic Risk Score Predicts Progression of Islet Autoimmunity and Development of Type 1 Diabetes in Individuals at Risk. *Diabetes Care* 41(9), 1887-1894. DOI: 10.2337/dc18-0087

3.5. Sharp, S.A., Rich, S.S., Wood, A.R., Jones, S.E., Beaumont, R.N., Harrison, J.W., Schneider, D.A., Locke, J.M., Tyrrell, J.**, Weedon, M.N.**, Hagopian, W.A. & **Oram, R.A**.

(2019) Development and Standardization of an Improved Type 1 Diabetes Genetic Risk Score for Use in Newborn Screening and Incident Diagnosis. *Diabetes Care* 42(2), 200-207. DOI: 10.2337/dc18-1785

3.6. Ferrat, L.A., Vehik, K., Sharp, S.A., Lernmark, A., Rewers, M.J., She, J., Ziegler, A-G., Toppari, J., Akolkar, B., Krischer, J.P., **Weedon, M.N., Oram, R.A. (joint senior)**, Hagopian, W.A. & TEDDY Study Group; Committees. (2020) A Combined Risk Score enhances prediction of Type 1 Diabetes Among Susceptible Children. *Nature Medicine* 26, 1247–1255. DOI: 10.1038/s41591-020-0930-4

4. Details of the impact

About 400,000 people in the UK suffer from type 1 diabetes, with acute and long-term complications leading to a significant excess of mortality and morbidity. Meeting these health care needs costs the NHS more than £1 billion per year. Our work has three main areas of impact around preventing and correctly diagnosing the disease.

4.1. Type 1 diabetes genetic risk score aids classification of diabetes and improves treatment

Misclassification of diabetes is common, because no single presenting feature (such as age, body mass index, or autoantibody positivity) perfectly distinguishes the main diabetes types. Different types of diabetes are treated in very different ways, yet the misclassification rate at diagnosis is over 15%. This leads to needless, harmful and costly treatments being given to patients. Incorrect treatment also reduces patient quality of life and increases the risk of acute and chronic diabetes complications. The T1D GRS aids reduction of these problems by discriminating type 1 diabetes from type 2 diabetes, and from single gene diabetes.

The Exeter team has integrated this approach into the (Exeter based) NHS diabetes genetics diagnostic testing service, which provides genetic testing both in the UK and across the world [**5.1**]. The T1D GRS has been used in over 2,000 diagnoses over the past 2 years [**5.2**]. Uptake by clinicians is increasing quickly, and to meet this rising demand the University of Exeter has partnered with the healthcare diagnostics company, Randox to develop a simple biochip test that can be run rapidly in a clinical diagnostic department [**5.3**]. The company has already invested around £200,000 in the biochip and plans to make it commercially available in 2021 (delayed due to Covid pandemic – see mitigation statement).

4.2. T1D GRS helps to prevent death and disability from diabetic ketoacidosis

Children diagnosed with type 1 diabetes in early life have a 40% risk of life-threatening ketoacidosis at diagnosis. Autoantibody measurements can predict who will get type 1 diabetes and reduce emergency presentation with severe diabetic ketoacidosis from about 40% to less than 10%, but it is too expensive for widespread population screening.

The Exeter team's combined risk score, including the T1D GRS, makes public health screening economically viable. Firstly, it restricts follow-up to those 10% of newborns with a high genetic risk of type 1 diabetes, measured using the Exeter developed blood spot T1D GRS assay [**3.6**]. Secondly, it targets follow-up at those within this high-risk group who are most likely to get type 1 diabetes. This combined approach has been used to develop a neonatal heel prick blood spot test that is being used in two health screening studies in the USA, to help prevent early life diabetic ketoacidosis. These studies are called CASCADE (led by the Pacific Northwest Diabetes Research Institute in Washington State [**5.4**]), and PLEDGE (led by Sanford Health, a non-profit healthcare provider [**5.5**]).

4.3. T1D GRS kick-starts vaccine trials in infants

Trials of vaccines to prevent type 1 diabetes have been limited by an inability to easily identify high-risk babies. A genetic test called human leukocyte antigen (HLA) typing has

previously been used in this context but could only identify babies with more than 5% risk of developing the disease. In contrast, the Exeter team collaborated with a group at the Technical University of Munich to show that the T1D GRS offers a cheaper, more accurate way to predict which newborns have a greater than 10% risk of developing type 1 diabetes. This potentially halves the number of participants needed for early-life intervention trials [**3.3**].

Using the T1D GRS, the $52M Global Platform for the Prevention of Autoimmune Diabetes (GPPAD) the first early life pan-European trial of a type 1 diabetes vaccine began in 2017, and aims to screen 500,000 newborns [**5.6**]. So far, more than 200,000 newborn babies have had heel prick blood testing using the T1D GRS, and more than 400 of them have enrolled in the trial and the trial is on track to screen 330,000 newborns by 2022 [**5.7**].

5. Sources to corroborate the impact

5.1: Website for researchers and clinicians to request the genetic risk score test : https://web.archive.org/web/20201218111226/https://www.diabetesgenes.org/tests-for-diabetes-subtypes/type-1-diabetes-genetic-risk-score/;
Clinical calculator that incorporates the GRS for classifying diabetes subtype: https://web.archive.org/web/20201218111230/https://www.diabetesgenes.org/t1dt2d-prediction-model/

5.2: Letter from Clinical Scientist at Exeter Diabetes Diagnostic Service, detailing the number of GRS tests requested in 2019 and 2020

5.3: Letter from head of R&D at Randox, detailing the collaboration with Exeter and the company's substantial investment in developing a genetic risk score biochip.

5.4: Supporting letters from CASCADE investigators and funders (Janssen Pharmaceuticals & Director of Diabetes Programme, Pacific Northwest Diabetes Research Institute, University of Washington) detailing how Exeter's work has influenced their decision to bring the genetic risk score into clinical practice.

5.5: Supporting letter from PLEDGE investigators at Sanford Health detailing how Exeter's work has influenced their decision to bring the genetic risk score into clinical practice.

5.6: GPPAD (www.gppad.org), Winkler, C., Haupt, F., Heigermoser, M., Zapardiel-Gonzalo, J., Ohli, J., Faure, T., Kalideri, E., Hommel, A., Delivani, P., Berner, R., Kordonouri, O., Roloff, F., von dem Berge, T., Lange, K., Oltarzewski, M., Glab, R., Szypowska, A., Snape, M.D., Vatish, M., Todd, J.A., Larsson, H.E., Ramelius, A., Kördel, J.Å., Casteels, K., Paulus, J., Ziegler, A.G., Bonifacio, E. & GPPAD Study Group. (2019) Identification of infants with increased type 1 diabetes genetic risk for enrollment into Primary Prevention Trials-GPPAD-02 study design and first results. *Pediatr. Diabetes* 20(6), 720-727. DOI: 10.1111/pedi.12870. PMID: 31192505

5.7. Press release announcing 100,000 babies screened in GPPAD study (31/07/2019) https://www.helmholtz-muenchen.de/hdc/service/news/news/article/46585/index.html